Cyclization of Diethyl 2-Acetoacetyl-3-oxoglutarate Anion generated *in situ* by the Reaction of Diethyl Sodio-3-oxoglutarate with Diketen

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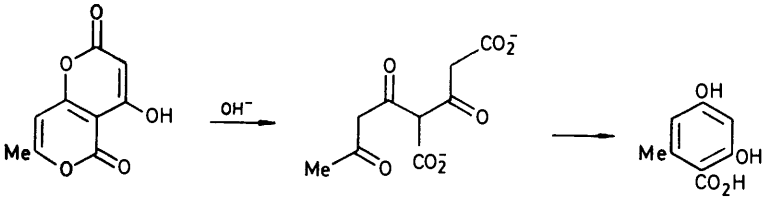
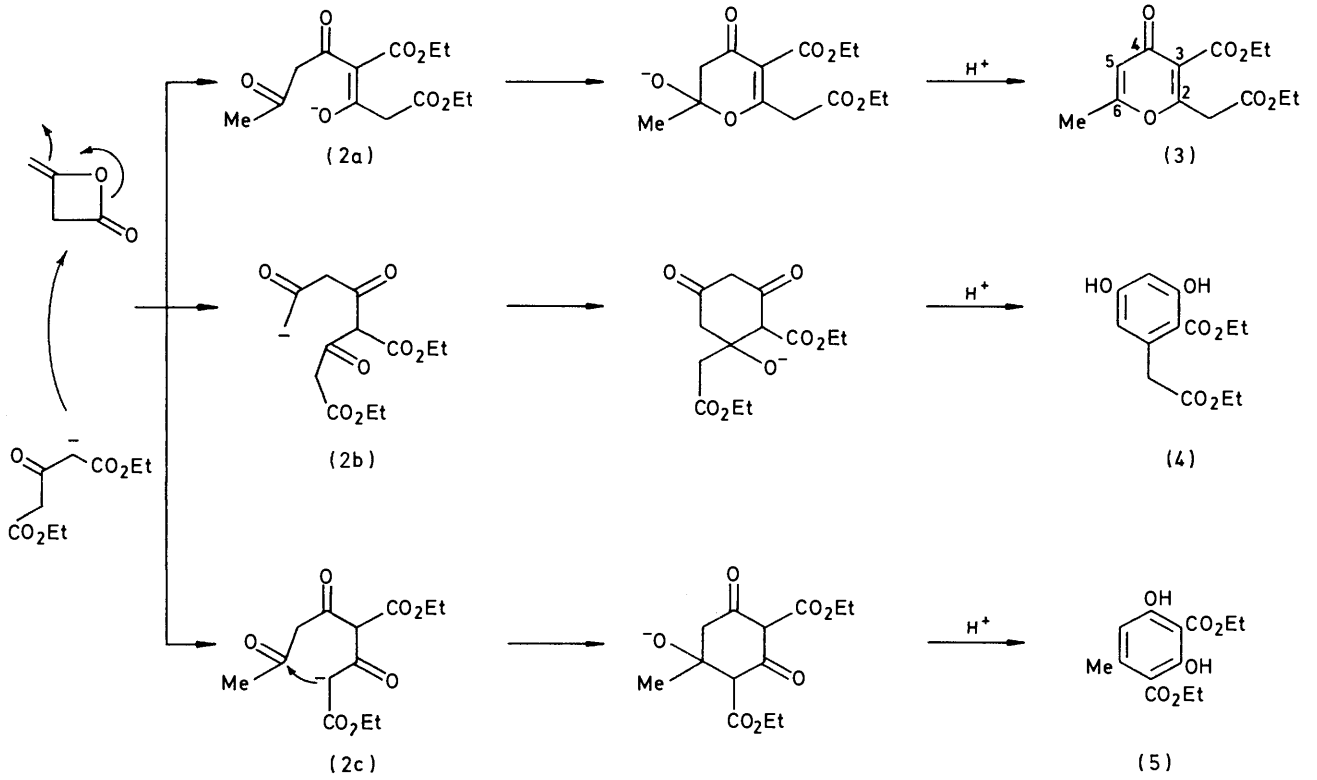
Reaction of diethyl sodio-3-oxoglutarate with diketen (4-methyleneoxetan-2-one) in anhydrous tetrahydrofuran under mild conditions provided an intermediate adduct (diethyl 2-acetoacetyl-3-oxoglutarate anion) (2), which immediately cyclized to a γ-pyrone (ethyl 3-ethoxycarbonyl-6-methyl-4-oxo-4*H*-pyran-2-ylacetate) (3), regarded as a masked form of tetra-acetic acid (3,5,7-trioxo-octanoic acid) (1), and three aldol-type condensation products [ethyl 2-ethoxycarbonyl-3,5-dihydroxyphenylacetate (4), diethyl 2,6-dihydroxy-4-methylisophthalate (5), and ethyl 3-acetyl-2,6-dihydroxy-4-methylbenzoate (6)].

TETRA-ACETIC ACID LACTONE and some naturally occurring phenolic compounds, *e.g.* orsellinic acid, orcinol, and 6-methylsalicylic acid, are thought to be biosynthesized from the enzyme-bound thiol ester of tetra-acetic acid (3,5,7-trioxo-octanoic acid). Syntheses of tetra-acetic acid derivatives and their biomimetic conversions into phenolic compounds of the natural type have been carried out extensively.[1] For example Harris and his co-workers have synthesized tetra-acetic acid from the trianion of diacetylacetone by ω-carboxylation with carbon dioxide.[2]



(1)

SCHEME 1



(2a) (2b) (2c) (3) (4) (5)

SCHEME 2

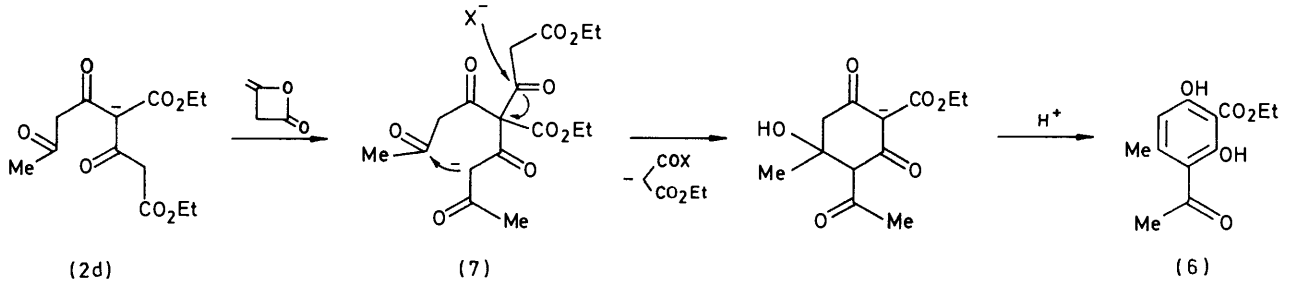
The methyl ester of tetra-acetic acid has been transformed into orsellinic acid and acetylphloroglucinol by aldol- and Claisen-type condensations, respectively. The pyranopyran (1), regarded as a masked form of

[1] T. Money, *Chem. Rev.*, 1970, **70**, 553 and references cited therein.

[2] T. T. Howarth, G. P. Murphy, and T. M. Harris, *J. Amer. Chem. Soc.*, 1969, **91**, 517.

tetra-acetic acid, has been prepared from triacetic acid lactone by Money *et al.*[3] On treatment with alkali, the dipyrone (1) underwent recyclization to orsellinic acid *via* an intermediate trioxo-diacid anion as shown in Scheme 1. In these cyclizations under basic conditions, one might reasonably expect to obtain α- or γ-pyrone derivatives[4,5] as well as aldol or Claisen condensation products, but such reactions have never been reported.

We have examined the cyclization of diethyl 2-acetoacetyl-3-oxoglutarate anion (2), corresponding to an open form of (1), generated by reaction of diethyl sodio-3-oxoglutarate with diketen. Addition of 2 equiv. of diketen to a cold solution of the sodio-diester in anhydrous tetrahydrofuran gave the expected γ-pyrone (3) and three resorcylic derivatives, (4)—(6). The γ-pyrone (3) showed strong i.r. absorption at 1 550 cm^{-1} (C=C of γ-pyrone) and proton n.m.r. signals at δ 2.26 (3 H, d, *J* 1 Hz, 6-Me), 3.59 (2 H, s, 2-CH_2), and 6.00 (1 H, q, *J* 1 Hz, H-5); on irradiation at the frequency of the vinylic H-5, the 6-methyl doublet was changed into a singlet.



SCHEME 3

The diester (4) may be produced by an unusual aldol-type condensation of the anion (2) in its less stable terminal form (2b), and the diester (5) by a similar aldol-type condensation of the form (2c). Compound (5) was converted into orcinol quantitatively by heating in aqueous 10% sodium hydroxide. The minor resorcylic product (6) may be formed *via* aldol condensation and simultaneous cleavage of a C_3 unit from an intermediate pentaoxo-diester (7) (see Schemes 2 and 3).

EXPERIMENTAL

^1H N.m.r. data were obtained with a JEOL JNM-ps-100 instrument for solutions in deuteriochloroform with tetramethylsilane as internal reference. I.r. spectra were recorded with a JASCO IR-1 spectrometer. Mass spectra were measured with a Hitachi RMU-6 instrument. Yields are based on starting material consumed.

Reaction of Diethyl Sodio-3-oxoglutarate with Diketen in Anhydrous Tetrahydrofuran.—Diethyl sodio-3-oxoglutarate [from diethyl 3-oxoglutarate (5.05 g, 0.025 mol) and sodium (0.575 g, 0.025 mol)] was dissolved in anhydrous tetrahydrofuran (30 ml) and cooled at −10 °C under nitrogen. A solution of diketen (4.20 g, 0.05 mol) in anhydrous tetrahydrofuran was added dropwise with stirring. Stirring was continued for 30 min at −10 °C, and the mixture was then brought to room temperature, neutralized with 5% hydrochloric acid, and extracted with ethyl acetate. The combined extracts were washed with brine, dried over (Na_2SO_4), and concentrated under reduced pressure. The viscous oily residue was separated by chromatography on silica gel [hexane–ethyl acetate (3 : 1) as eluant] to give (i) *ethyl 3-acetyl-2,6-dihydroxy-4-methylbenzoate* (6) (0.07 g, 1.4%), needles, m.p. 88—89° (from hexane); *m/e* 238 (M^+), 194 ($M^+ - 44$), 177 ($M^+ - 61$), and 164 ($M^+ - 74$); δ 1.44 (3 H, t, *J* 7 Hz), 2.53 (3 H, s), 2.76 (3 H, s), 4.44 (2 H, q, *J* 7 Hz), 6.29br (1 H, s), 13.61 (1 H, s, disappeared on adding D_2O), and 16.21 (1 H, s, disappeared on adding D_2O); $\nu_{max.}$ (Nujol) 3 400—3 200vw,br, 1 645sh,w, 1 638sh,w, 1 615, and 1 578 cm^{-1} (Found: C, 60.25; H, 5.95. $C_{12}H_{14}O_5$ requires C, 60.5; H, 5.9%), (ii) diethyl 2,6-dihydroxy-4-methylisophthalate (5) (1.12 g, 19.4%), needles, m.p. 61—62° (lit.,[6] 52—53°) (from hexane); *m/e* 268 (M^+), 222 ($M^+ - 46$), 178 ($M^+ - 90$), 177 ($M^+ - 91$), and 176 ($M^+ - 92$); δ 2.44 (3 H, s), 6.32 (1 H, s), 11.27 (1 H, s, disappeared on adding D_2O), and 12.12 (1 H, s, disappeared on adding D_2O); $\nu_{max.}$ (Nujol) 3 400—3 200vw,br, 1 660, 1 645, 1 578, 1 318, 1 255, 1 234, and 1 193 cm^{-1} (Found: C, 58.05; H, 6.05. Calc. for $C_{13}H_{16}O_6$: C, 58.2; H, 6.05%); (iii) diethyl 3-oxoglutarate (0.70 g); (iv) ethyl 2-ethoxycarbonyl-3,5-dihydroxyphenylacetate (4) (0.96 g, 16.6%), needles, m.p. 107—108° (lit.,[7] 108°) (from benzene); δ 3.84 (2 H, s), 6.16 (1 H, d, *J* 2 Hz), 6.80 (1 H, s, disappeared on adding D_2O); $\nu_{max.}$ (Nujol) 3 280, 1 703, 1 652, 1 597, and 1 575 cm^{-1}; *m/e* 268 (M^+), 223 ($M^+ - 45$), 222 ($M^+ - 46$), 194 ($M^+ - 74$), 167 ($M^+ - 101$), and 166 ($M^+ - 102$) (Found: C, 58.0; H, 5.95. $C_{13}H_{16}O_6$ requires C, 58.25; H, 6.0%); and (v) *ethyl 3-ethoxycarbonyl-6-methyl-4-oxo-4H-pyran-2-ylacetate* (3) (1.66 g, 28.8%), needles, m.p. 54—55° (from chloroform–hexane); $\nu_{max.}$ (Nujol) 1 743, 1 725, 1 718, 1 640, and 1 551 cm^{-1}; δ 2.26 (3 H, d, *J* 1 Hz), 3.59 (2 H, s), and 6.00 (1 H, q, *J* 1 Hz) (Found: C, 58.25; H, 6.0. $C_{13}H_{16}O_6$ requires C, 58.2; H, 6.0%); *m/e* 268 (M^+).

Conversion of the Diester (4) *into Orcinol.*—Compound (4) (0.21 g) dissolved in aqueous 10% sodium hydroxide (10 ml) was refluxed under nitrogen. After 1 h the mixture was acidified with 2% hydrochloric acid and extracted with ethyl acetate. The combined extracts were washed with brine, dried (Na_2SO_4), and distilled to leave orcinol in quantitative yield, identical with a commercial sample.

[6/1184 *Received*, 21*st June*, 1976]

[3] T. Money, F. W. Comer, G. R. B. Webster, I. G. Wright, and A. I. Scott, *Tetrahedron*, 1967, **23**, 3435.
[4] E. Suzuki, H. Sekizaki, and S. Inoue, *Synthesis*, 1975, 652.
[5] T. Kato and T. Hozumi, *Chem. and Pharm. Buli.* (*Japan*), 1972, **20**, 1574.
[6] D. S. Jerdan, *J. Chem. Soc.*, 1899, **75**, 808.
[7] H. Nogami, *Yakugaku Zasshi*, 1941, **61**, 24.